Association Between Estimated Pulse Wave Velocity and the Risk of Cardiovascular Outcomes in Men

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Carotid-femoral pulse wave velocity (cfPWV) by direct measurement with tonometry is the gold standard means for assessing aortic stiffness and is associated with adverse cardiovascular disease (CVD) outcomes.[1] Equations using age and mean blood pressure (BP) may be useful to estimate PWV (ePWV) [2] and have been shown to predict all-cause and CVD mortality in individuals with hypertension,[3] but its predictive capacity for CVD outcomes has yet to be tested more broadly in the general population. The purpose of this study was to evaluate whether ePWV would be associated with CVD outcomes and mortality.

This prospective study was based on the general population sample of 2,666 middle-aged Caucasian men (aged mean SD 53.1±5.1, range 42-61 years) in the Kuopio Ischemic Heart Disease cohort study. ePWV was calculated from an equation based on age and mean blood pressure (MBP).[2,3] Levels of ePWV were categorized according to quartiles (<8.5 [the lowest], 8.5-9.2, 9.2-10.0, and >10.0 m/s [the highest]).[2,5] Cardiovascular outcomes were operationally defined as cardiovascular mortality (CVM), sudden cardiac death (SCD) and atrial fibrillation (AF). All-cause mortality (ACM) was also assessed. We used Cox proportional hazard adjusted models to determine the hazard ratios (HRs) and 95% confidence intervals (CIs) of ePWV for outcomes. To further evaluated whether ePWV would be associated with an improvement in the prediction of CVM risk using the Systematic Coronary Risk Evaluation (SCORE) algorithm (comprising of age, sex, smoking status, SBP, total cholesterol, and HDL-C) and the Framingham CVD Risk Score (FRS) (comprising of age, sex, smoking status, SBP, total cholesterol, HDL-C and diabetes status), we calculated measures of discrimination (using Harrell's C-index and difference in -2 log likelihood) and reclassification (using net-reclassification-index, NRI and integrated-discrimination-improvement, IDI).[4]

During a median 25-year follow-up (interquartile ranges: 18-27 years), 1,274 ACM, 594 CVM, 255 SCD, and 511 AF events occurred, respectively. Cumulative hazard curves

demonstrated lower survival among males of ePWV value > 10.0 m/s compared to those of ePWV value < 10.0 m/s (P<0.001 for log-rank test; Figure 1).

After adjusting for CVD risk factors (Table 1), the highest levels of ePWV were significantly associated with an increased risk for ACM (hazard ratio [HR] 1.39, 95% Confidence Interval [CI]: 1.11-1.73), CVM (HR 1.79, 95% CI, 1.27-2.52), SCD (HR 1.86, 95% CI, 1.11-3.11), and AF (HR 1.46, 95% CI, 1.03-2.06), as compared with the lowest level of ePWV (reference). On addition of ePWV to SCORE, there was no significant increase in the C-index: -0.0001 (95% CI: -0.0012, 0.0010; p=0.82) and no significant improvement in the -2 log likelihood of the risk score with and without inclusion of ePWV (p for comparison=0.48). There was no significant improvement in the classification of participants into predicted 10-year CVM risk categories (NRI: 0.26%, -2.88, 3.40%; p=0.87). The IDI was -0.0001 (-0.0007, 0.0004; p = 0.62). For the FRS, the C-index change; -2 log likelihood p-value for comparison; NRI; and IDI were 0.0002 (95% CI: -0.0012, 0.0016; p=0.77); p for comparison=0.31; 1.03%, -1.57, 3.63%; p=0.44); and -0.0001 (-0.0010, 0.0007; p = 0.78) respectively.

These findings demonstrate that ePWV is related to CVD outcomes and mortality, independent of traditional CVD risk factors, in the general population. Individuals having an ePWV value > 10.0 m/s [5] were 79% more likely to die from CVD, 86% more likely to die from SCD and 46% more likely to suffer from AF compared to those with lower ePWV (<8.5 m/s). Our findings support the importance of elevated arterial stiffness as independently associated with AF risk[6] and add to the novel observation that elevated levels of arterial stiffness may also be associated with SCD risk. However, addition of ePWV to contemporary CVD risk scores such as SCORE and the FRS, did not improve discrimination of CVD mortality risk. A limitation of this study is that the cohort examined was exclusively men. Additional research examining the role of ePWV as a predictor of CVD events in women is warranted. These

findings demonstrate a potential role of arterial stiffness in identifying patients at high risk for adverse cardiovascular outcomes, but further evaluation is warranted in differing populations (general population vs. hypertensive) and racial/ethnic backgrounds. Finally, it should be evaluated whether ePWV (like cfPWV) is similarly and favorably modulated by different lifestyle and rehabilitation modalities such as exercise and sauna bathing[7].

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Table 1. The hazard ratio and 95% confidence interval for all-cause mortality, cardiovascular mortality, sudden cardiac death, and atrial fibrillation by ePWV quartiles (n=2,666).

ePWV	< 8.5 m/s (n=637)	8.5-9.2 m/s (n=643)	9.2-10.0 m/s (n=694)	>10.0 m/s (n=692)
All-cause mortality	1 (ref)	0.99 (0.80-1.22)	1.27 (1.03-1.57)	1.39 (1.11-1.73)
Cardiovascular mortality	1 (ref)	1.01 (0.79-1.54)	1.58 (1.13-2.19)	1.79 (1.27-2.52)
Sudden cardiac death	1 (ref)	1.11 (0.67-1.83)	1.57 (0.95-2.59)	1.86 (1.11-3.11)
Atrial fibrillation	1 (ref)	1.04 (0.76-1.44)	1.10 (0.79-1.53)	1.46 (1.03-2.06)

Adjusted for age, body mass index, smoking, diabetes, anti-hypertensive medication, total cholesterol, HDL-C, glucose, C-reactive protein, CVD history, alcohol intake, maximal oxygen uptake and family history of CVD. ePWV: estimated pulse wave velocity

Figure 1. The cumulative hazard curves for all-cause mortality and cardiovascular mortality by ePWV value > 10.0 m/s.